A patient-specific model for convection enhanced radio-lipsome delivery

Ryan T. Woodall[1,2], David A. Hormuth II[2], Xinzeng Feng[2], William T. Phillips[3], Ande Bao[3], Andrew J. Brenner[3], Thomas E. Yankeelov[1,2,4]

The University of Texas at Austin, Department of Biomedical Engineering[1],
The University of Texas at Austin, Center for Computational Oncology[2],
The University of Texas San Antonio Health Science Center[3],
The University of Texas at Austin, Dell Medical School[4]

Introduction

Re[186]-liposome brachytherapy is a new method for the treatment of glioblastoma multiforme (GBM), currently in clinical trials[1,2].

- Liposomes delivered via convection-enhanced delivery (CED).
- Re[186] kills cancer cells through radioactive β-decay.
- Slow, strong dose to delivery region
  - Re[186] half-life: **3.72 days**
 - β particle mean path-length: **2 mm**

- Safe dose for external beam radiation therapy[1]:
  70 Gy
- Safe dose for Re[186]-liposome brachytherapy[1]:
  >1800 Gy

Goal:

Develop, calibrate, and validate an advection-diffusion-reaction finite element model of nanoparticle delivery for predicting the optimal delivery location:

- Patient Specific
- Imaging informed
- Low computational resources required

Workflow
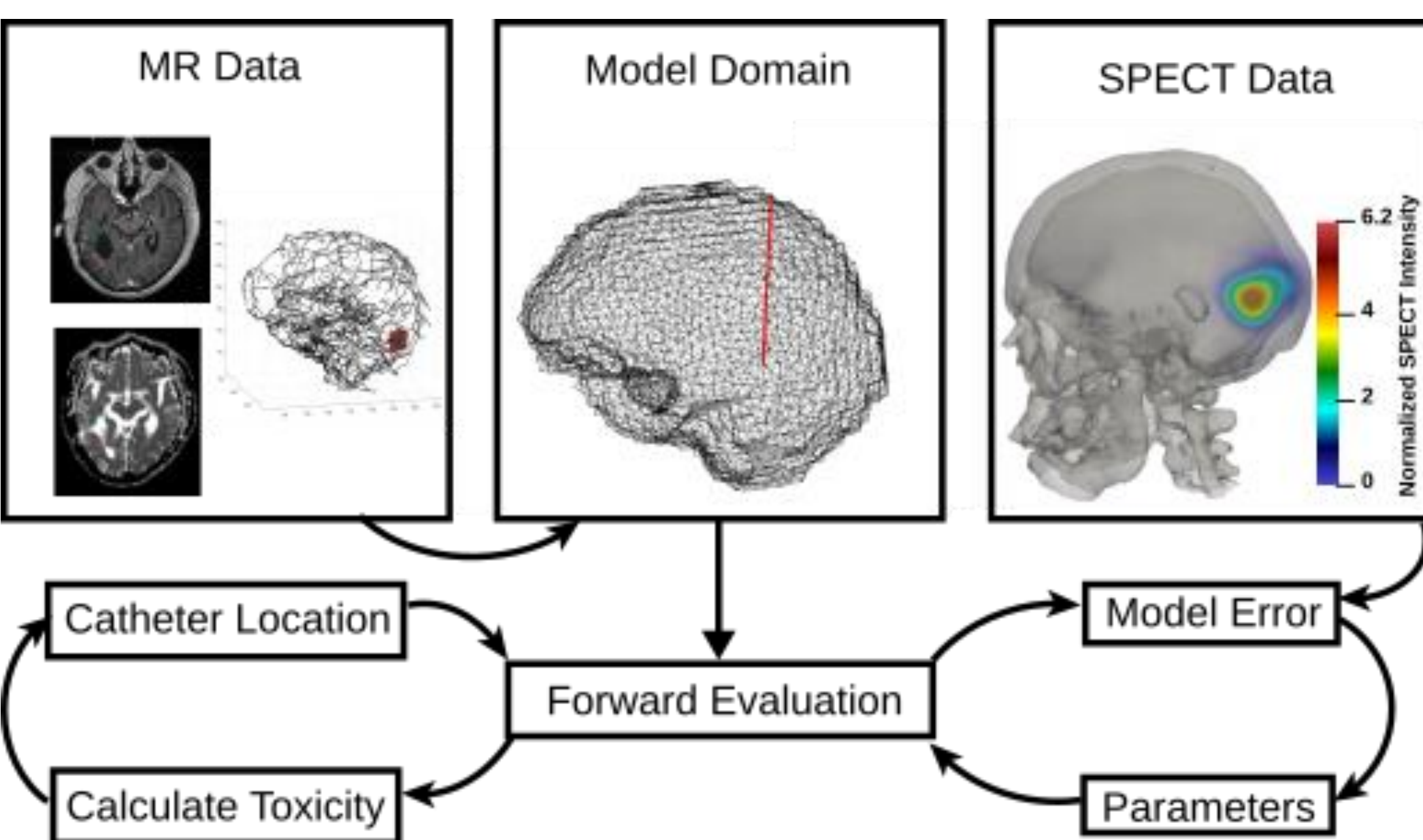
References:
[1]Phillips *et al.* 2012, *Neuro Oncology*
[2]Floyd *et al.* 2015, *Neuro Oncology*
[3]Rosenbluth *et al*, 2012, *NeuroImage*

Imaging Methods

- Use medical imaging techniques and mathematics to model liposome distribution
- T_1, T_1+C highlights regions of vasculature
  - Vasculature → blood clearance
- Diffusion-weighted MRI measures the apparent diffusivity of water (ADC)
  - ADC → scale liposome diffusion
- SPECT/CT measures local Re[186] radiation
  - Ground truth
- Reaction-Diffusion model with varying complexity

T1+C   ADC   SPECT/CT
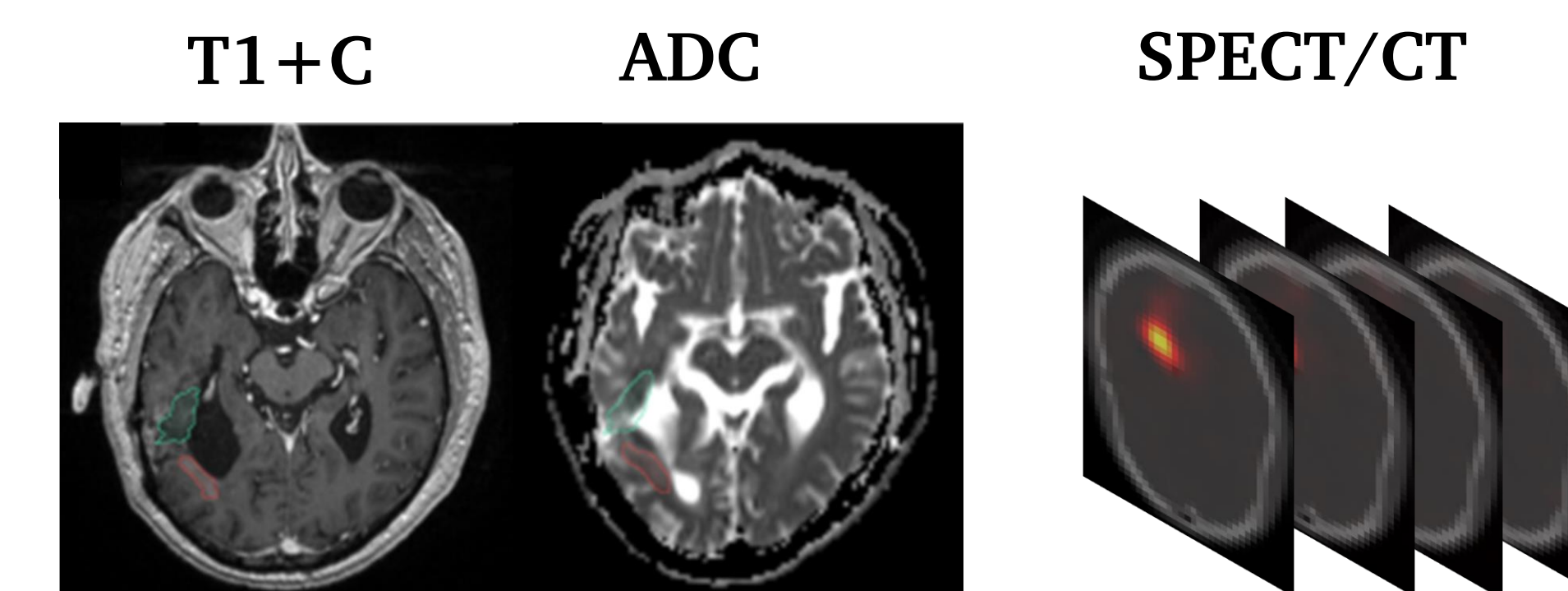
Numerical Methods

Mesh Generation
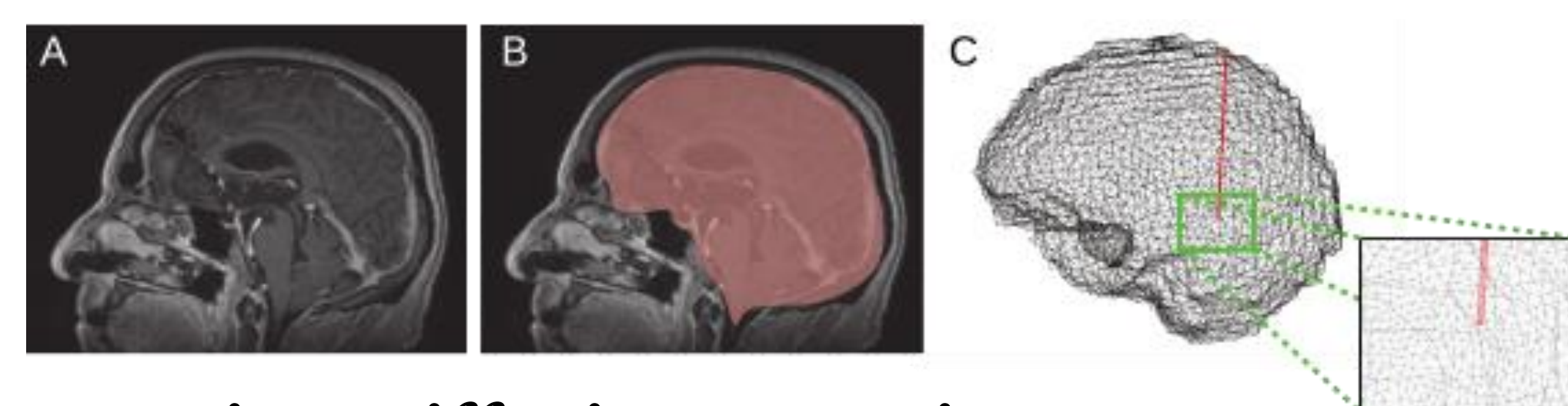
Reaction-Diffusion Equation

$$\frac{\delta C}{\delta t} = \nabla \cdot D\nabla C - R \cdot \frac{S}{V}$$

ADC-Damped Diffusion

$$D = D_0 \exp\left(-\frac{ADC}{\gamma}\right)$$

Perfusion-Informed Clearance

$$\frac{S}{V} = \frac{T_{1,post} - T_{1,pre}}{T_{1,post}}$$

C, concentration of liposome

D, apparent diffusivity of liposomes

D_0, base liposome diffusivity

ADC, apparent diffusivity of water (diffusion-weighted MRI)

γ, scaling factor

R, flow rate into vasculature

$\frac{S}{V}$, ratio of vascular surface area to vascular volume
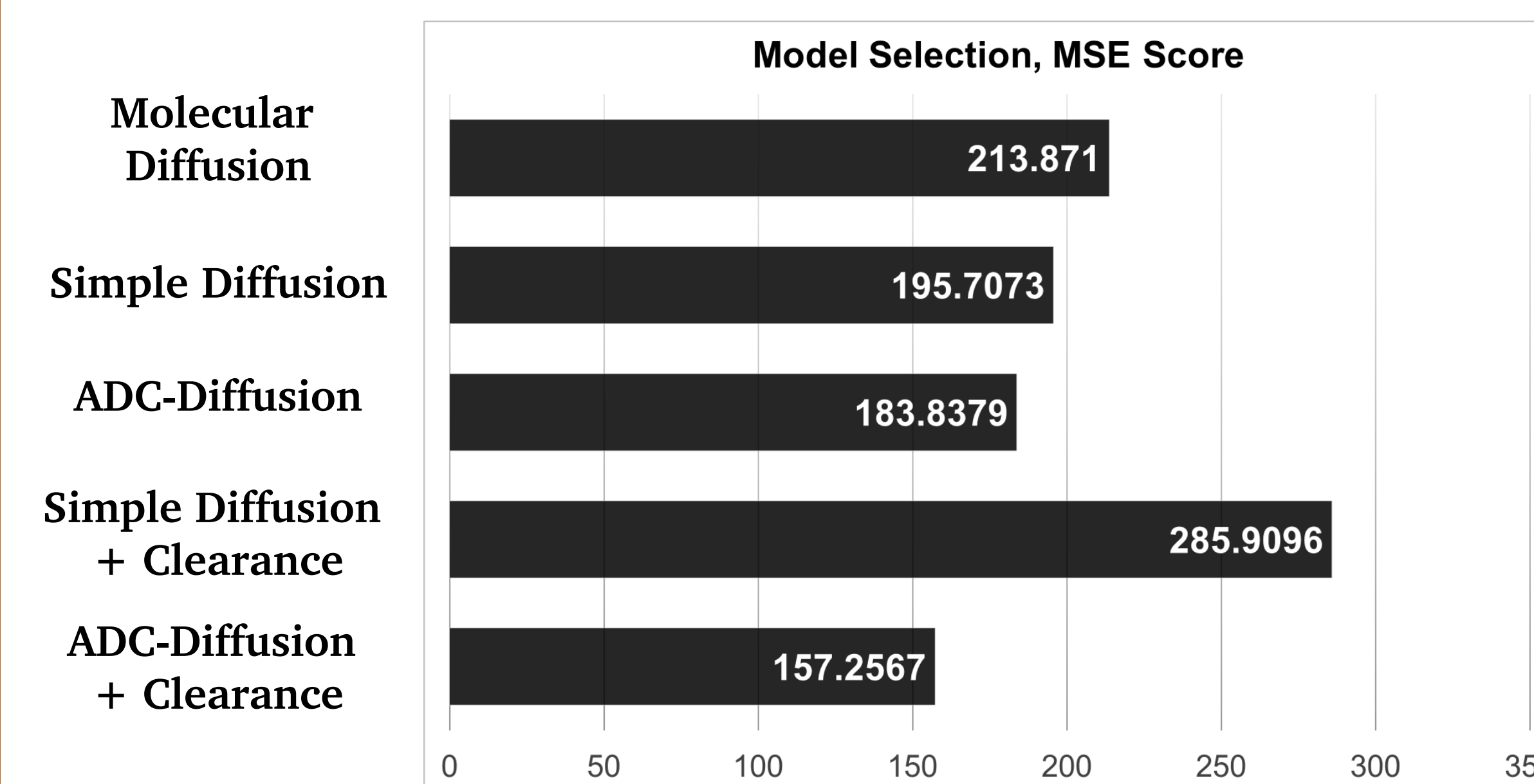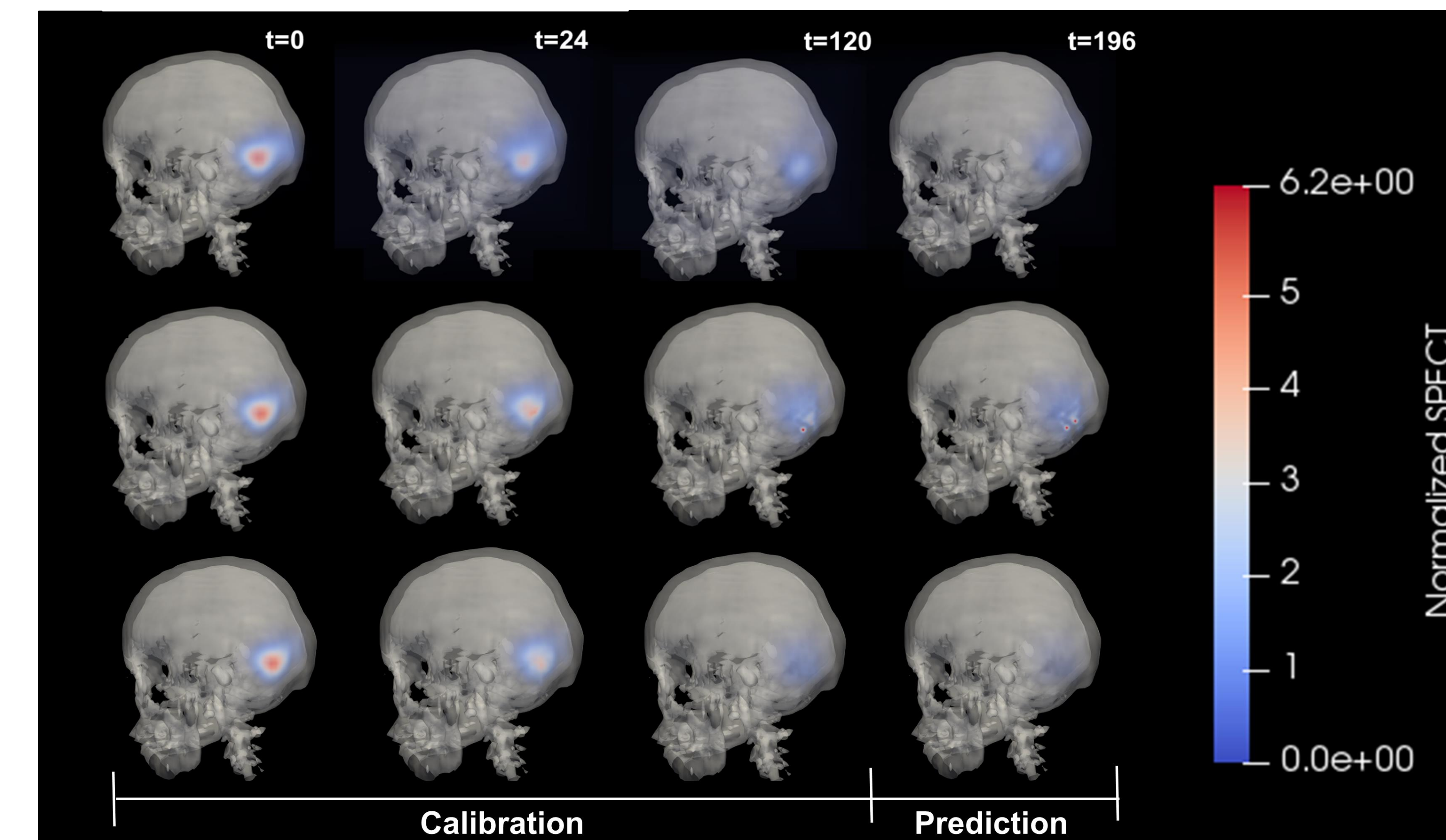
$T_{1,post/pre}$, T_1 before and after contrast (T_1 MRI)

Results – Single Patient

Normalized SPECT (ground truth)

ADC-Damped Diffusion

ADC-Damped Diffusion + Perfusion-Informed Clearance

Model Calibration and Complexity Analysis

- Ground-truth: SPECT/CT

- 5 Models tested
  - Molecular Diffusion (D=2.6E-4mm^2)
  - Simple Diffusion (D calibrated)
  - ADC-Diffusion (D_0, gamma calibrated)
  - Simple Diffusion + Clearance (D, R calibrated)
  - ADC-Diffusion + Clearance (D_0, γ, R calibrated)

- Models all calibrated through 120 hrs, and projected forward to 196 hrs

- Error measured as mean-squared error (MSE)

Model Selection, MSE Score

Model	MSE Score
Molecular Diffusion	213.871
Simple Diffusion	195.7073
ADC-Diffusion	183.8379
Simple Diffusion + Clearance	285.9096
ADC-Diffusion + Clearance	157.2567

Future Directions + Conclusion

These results demonstrate the ability of our model to model the transport of radioactively-labeled liposomes within the brain, in comparison to software currently in use. As the ADC-Diffusion model, with clearance is the most accurate at predicting the final SPECT time point, we have selected this model for future work. Future work will focus on modeling the initial delivery of the Re[186]-liposomes, and utilize the calibrated parameters selected for this model. Ultimately, we will use this tool to predict the localize radioactive dose absorbed within the brain, and optimize the injection location to maximizes effective dose.